REMARKS

A check for the requisite fee for a three month extension of time accompanies this response. Any fees that may be due in connection with this paper or this application may be charged to Deposit Account No. 50-1213. If a Petition for extension of time is needed, this paper is to be considered such Petition.

Claims 1, 5, 9-11, 15-17, 21, 23, 25-32, 42, 74-77, 82-84, 88 and 89 are presently pending in this application. Claims 2, 4, 6, 8, 12-14, 18-20, 23-24, 33-40, 43-48, 50-73, 85-87 and 90-92, which are directed to subject matter that is withdrawn from consideration as being drawn to non-elected subject matter, are cancelled without prejudice or disclaimer. Claims 3 and 41 are also cancelled without prejudice. Applicant reserves the right to file divisional applications to the non-elected subject matter and continuations to any cancelled subject matter. Claim 88 and 89 are retained pending reconsideration of the restriction requirement as between these claims and group I.

Claims 1, 5, 9, 15, 27, 29, 31, 32, 42, 49, 74, 76, 77, 82 and 83 are amended to conform to the restriction requirement, to more particularly point out the subject matter of the claim or to correct minor obvious errors. None of the amendments to the claims have been made in order to narrow the scope thereof of the claim nor to overcome prior art. The amendments are designed to change the form, not the substance, of the claims.

Claims 82-84 are objected to because claim 82 depends from non-elected claim 78, and claims 83-84 depend from claim 82. Claim 82 is rewritten as an independent claim, thereby obviating this objection.

A marked up copy per 37 C.F.R. §1.121 of the amended claims is attached to this response.

Requirement for restriction

Applicant acknowledges that the Restriction Requirement has been made FINAL, and that Group I claims, elected by Applicant, have been examined. Applicant respectfully urges that restriction between groups XI and I is improper. Group XI, claims 88 and 89, are directed to transgenic nematodes that comprise a mutant LOV-1 gene; group I, includes claims, such as claim 15, which is directed to a mutant LOV-1 gene.

The claims of groups XI claim 88 and 89) and I, thus, are related as a combination (nematodes containing the mutated gene) and a subcombination (the mutated gene). As between subject matter related as combination/subcombination **two-way** distinctness, which is absent in this instance, is required.

Inventions that are related as a combination and subcombination are distinct and restriction may be proper **only if** it can be shown that the combination as claimed does not require the particulars of the subcombination as claimed for patentability **and** that the subcombination has utility by itself or in other combinations. See MPEP 808.05(c).

Such two way distinctness is lacking in this case. In this instance, patentability of the combination, the transgenic nematode, requires the particulars of the subcombination, the mutated LOV-1 gene of group I, for patentability. In addition the subcombination, the mutant gene use by itself in other combinations, such as in cells for *in vitro* assays.

If the claims are divided into these two groups, applicant ultimately could be granted two patents, one directed to the nematode containing the mutant gene, and the other to the mutant gene, that are not required to be co-owned and that could expire on different dates. Thus, for example, if the claims to the combination, the transgenic nematodes containing the mutant gene, issued first, a later issuing patent encompassing the subcombination, the mutant gene,

could not be held to constitute obvious-type double patenting over the earlier issuing patent. See MPEP 806, paragraph 3, which states:

> [w]here inventions are related as disclosed but are not distinct as claimed, restriction is never proper. Since, if restriction is required by the Office double patenting cannot be held, it is imperative the requirement should never be made where related inventions as claimed are not distinct.

See, also MPEP 804.01, which states:

> 35 U.S.C.121, third sentence, provides that wherein the Office requires restriction, the patent of either the parent or any divisional application thereof conforming to the requirement cannot be used as a reference against the other. This apparent nullification of double patenting as ground of rejection or invalidity in such cases imposes a heavy burden on the Office to guard against erroneous requirements for restriction where the claims define essentially the same inventions in different language and which, if acquiesced in, might result in the issuance of several patents for the same invention.

Therefore, as between groups XI and I, the restriction requirement is improper. Accordingly, group XI, claims 88 and 89, remain pending.

THE REJECTION OF CLAIMS 1, 3, 5, 9-11, 15-17, 21-22, 25-32, 41-42, 49, 74-77 and 82-84 UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

The Enablement Rejections

Claims 1, 3, 5, 9-11, 15-17, 21-22, 25-32, 41-42 and 49 are also rejected under 35 U.S.C. § 112, first paragraph because it is alleged that the specification, while being enabling for the nucleotide sequence set forth in SEQ ID NO. 3 isolated from *C. Elegans*, does not reasonably provide enablement for any and all homologs of SEQ ID NO. 3 isolated from any and all nematodes, any and all mutant forms of SEQ ID NO. 3, or any gene comprising the nucleotide sequence set forth in SEQ ID NO. 3. Reconsideration of the grounds for this rejection is respectfully requested in view of the amendments herein and the following remarks.

Relevant law

To satisfy the enablement requirement of 35 U.S.C § 112, first paragraph, the specification must teach one of skill in the art to make and use the invention without undue experimentation. Atlas Powder Co. v. E.I. DuPont de Nemours, 750 F.2d 1569, 224 USPQ 409 (1984). This requirement can be met by providing sufficient disclosure, either through illustrative examples or terminology, to teach one of skill in the art how to make and how to use the claimed subject matter without undue experimentation. This clause does not require "a specific example of everything *within the scope* of a broad claim." In re Anderson, 176 USPQ 331, at 333 (CCPA 1973), emphasis in original. Rather, the requirements of § 112, first paragraph "can be fulfilled by the use of illustrative examples **or** by broad terminology." In re Marzocci et al., 469 USPQ 367 (CCPA 1971)(emphasis added).

Further, because "it is manifestly impracticable for an applicant who discloses a generic invention to give an example of every species falling within it, or even to name every such species, it is sufficient if the disclosure teaches those skilled in the art what the invention is and how to practice it." In re Grimme, Keil and Schmitz, 124 USPQ 449, 502 (CCPA 1960). Thus, there is no doubt that a patentee's invention may be broader than the particular embodiment shown in the specification. A patentee not only is entitled to narrow claims particularly directed to the preferred embodiment, but also to broad claims that define the invention without a reference to specific instrumentalities. Smith v. Snow, 294 U.S. 1, 11, 24 USPQ 26, 30 (1935).

Thus, there is no requirement for disclosure of every species within a genus. Applicant is entitled to claims are commensurate in scope not only with what applicant has specifically exemplified, but commensurate in scope with that which one of skill in the art could obtain by virtue of that which the applicant has disclosed.

The inquiry with respect to scope of enablement under 35 U.S.C. §112, first paragraph, is whether it would require undue experimentation to make and use the claimed invention. A considerable amount of experimentation is permissible, particularly if it is routine experimentation. The amount of experimentation that is permissible depends upon a number of factors, which include: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, and the breadth of the claims. Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int'f 1986); see also In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988).

Analysis

Scope of the claims

The claims are directed to nucleic acids that encode the a *LOV-1* from *Caenorhabditis*. The claims specify that a *Caenorhabditis elegans* is *Caenorhabditis elegans* expressing the encoded LOV-1 protein exhibits normal location of vulva and response male nematode sensory behaviors. The claims further recite that the mutant genes are those that confer alterations in these behaviors. It is respectfully submitted that it would not require undue experimentation to isolate genes from *Caenorhabditis* species and identify those that encode a *LOV-1* protein by conferring a wild-type phenotype in a *Caenorhabditis elegans* that expresses such protein. Furthermore, it would not require undue experimentation to identify mutations in such gene that result in altered behavior.

Teachings of the specification

The specification describes identification and isolation of the *lov-1* gene from an exemplary nematode, *C. Elegans*, the characterization of *lov-1* mutants, wild-type and mutant LOV-1 proteins encoded by the *lov-1* gene and mutants thereof, the discovery of a correlation between *lov-1* gene expression and

observable mating behavior phenotypes, and the use of this discovery in methods to identify genes involved in the etiology of polycystic kidney disease.

The instant application describes and exemplifies in great detail methods for isolating nematode genes, for introducing mutations into nematode genes and for preparing transgenic nematode species.

Further, the specification sets forth assays that correlate expression of *lov-1 Caenorhabditis elegans* nematode mutants with defective mating behaviors, and assays are provided for identification of such mutants.

Level of skill

The level of skill in this art is recognized to be high (see, *e.g.*, Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int'f 1986)). The numerous articles and patents made of record in this application address a highly skilled audience and further evidence the high level of skill in this art.

Knowledge of those of skill in the art

At the time of the effective filing date of this application and before, the skilled artisan knew of standard methods for isolating and characterizing vertebrate homologs of nematode genes. There is a large body of literature directed to nematode biology and the identification and cloning of nematode genes, the correlation of the genes with mammalian genes, and the use of mutants of genes in assays for characterization of the genes and the related mammalian genes. For instance, Bargmann *et al.*, *Science*, 282:2028-2033 (1998) discusses that the *C. Elegans* homologs of highly conserved neuronal genes and human disease genes are open to standard methods for isolating mutations and characterizing gene networks by enhancer and suppressor analysis. Brenner, *Genetics*, 77:71-94 (1974), copy attached hereto, describes methods for the isolation, complementation and mapping of *C. Elegans* mutants. A review by the *C. Elegans* Sequencing Consortium of the Washington University Genome Sequencing Center describes the utility of the complete

genomic sequence of *C. Elegans* as a platform for investigating biology (*Science*, 282:2012-2018 (1998)).

Further, nematode species that are related to *C. Elegans* are often used in experimental systems to study development at the cellular, genetic and molecular levels. For instance, the aforementioned "Sequencing Consortium" *Science* article describes how, in analyzing the *C. Elegans* sequence, computer-generated gene structure predictions were refined using genomic sequence data from the related nematode *C. Briggsae* (see, page 2013, second full paragraph, col. 2). Further, Sommer *et al.*, Developmental Biology, 173:396-407 (1996) reviews how an understanding of vulval development in *C. Elegans* can be extended to analyze development at the cellular, genetic and molecular levels of three other species of nematodes. Hence those of skill in the art are familiar with a variety of nematode species and manipulation of the genes in those species and recognize the relatedness among species of the genus *Caenorhabditis*.

Presence of working examples

The specification provides working examples and description of the identification of the *lov-1* gene and its correlation to mating behavior and the use of transgenic and wild-type nematodes for the study of the gene.

Conclusions

In view of the extensive understanding of nematode biology, particularly of *Caenorhabditis* species, the breadth of the claims, the high level of skill in the art, the knowledge of those of skill in the art, and the description in the specification, it would not require undue experimentation for the skilled artisan to isolate the *lov-1* gene from other *Caenorhabditis* species and to make mutants thereof that alter mating behavior in *Caenorhabditis elegans*.

Claims 27-32, 41, 42, 49, 74-77, and 82-84

Claims 27-32, 41, 42, 49, 74-77, and 82-84 are rejected under 35 U.S.C. § 112, first paragraph, because it is alleged that the specification, while being enabling for a mutant *C. Elegans* that comprises a mutant *lov-1* gene exhibiting a phenotype of defective mating behavior particularly in the male sensory behaviors response and location of vulva, does not reasonably provide enablement for any and all transgenic nematodes comprising a vector encoding the nucleic acid sequence set forth in SEQ ID NO. 3, or any species of the nucleic acid sequence set forth in SEQ ID NO. 3, or any nucleic acid that encodes a mutated LOV-1 protein. The Examiner acknowledges that the specification provides extensive teachings pertaining to the isolation and characterization of the LOV-1 nucleic acid sequence and mutagenized *C. Elegans*. The Examiner however alleges that the specification fails to provide any relevant teachings or specific guidance with regard to the generation of any and all transgenic nematodes comprising a transgene comprising a LOV-1 nucleic acid molecule, in particular an animal that expresses (or over expresses) the transgene such that a disease phenotype occurs. The Examiner further states that the specification fails to even describe any particular phenotype exhibited by a transgenic nematode other than a transgenic mutant of C. Elegans, which, the Examiner acknowledges, has been rescued of the defective mating behavior phenotype, particularly in the male sensory behaviors response and location of vulva. In the Examiner's estimate, the specification fails to enable the production of any transgenic nematode for studying the etiology of polycystic kidney disease and identifying genes and factors involved in the disease pathway.

The Examiner further alleges that absent any relevant teachings or guidance in the specification with regard to the production of any transgenic nematode as claimed, one of skill in the art would not be able to rely on the

state of the transgenic art for an attempt to produce LOV-1 transgenic nematodes.

The Examiner cites several references to support his contention that the state of the art of transgenics is not a predictable art with respect to transgene behavior and the resulting phenotype. These references include the following: **Wall** (Theriogenology, 1996), which allegedly states that "[o]ur lack of understanding of essential genetic control elements makes it difficult to design transgenes with predictable behavior" (page 61, last paragraph). **Houdebine** (Journal of Biotechnology, 1994), which allegedly discloses that in the field of transgenics, constructs must be designed case by case without general rules to obtain good expression of a transgene (page 275, column 1, first paragraph).

Other references are cited by the Examiner to demonstrate that transgene expression in different species of non-human animals is not predictable and varies according to the particular host species, and specific promoter/gene combination(s). These include **Hammer *et al.*** (Journal of Animal Science, 1986), which allegedly reports that of transgenic mice, sheep and pigs containing the human growth hormone gene, expression of the gene resulting in growth was only found in mice; **Ebert *et al.*** (Molecular Endocrinology, 1988); **Mullins *et al.*** (Journal of Clinical Investigations, 1996) which allegedly states that " a given construct may react very differently from one species to another" (page S39, Summary); **Wall *et al.***, which allegedly reports "transgene expression and the physiological consequences of transgene products in livestock are not always predicted in transgenic mouse studies" (page 62, first paragraph); **Kappel *et al.*** (Current Opinion in Biotechnology, 1992), which allegedly discloses the existence of inherent cellular mechanisms that may alter the pattern of gene expression such as DNA imprinting, resulting from differential CpG methylation (page 549, column 2, third full paragraph); and **Strojek *et al.*** (Genetic Engineering, 1988) which allegedly points out that a high

degree of expression of a transgene in a mouse is often not predictive of high expression in other species such as pigs and rabbits. The Examiner concludes that given such species differences in the expression of a transgene, particularly when taken with the lack of guidance in the specification for the production of any and all transgenic nematodes whose genome comprises a *lov-1* transgene, it would require undue experimentation to predict the results achieved in any one host animal comprising and expressing a *lov-1* transgene, the levels of the transgene product, the consequences of that production, and, therefore, the resulting phenotype.

This rejection is respectfully traversed. It is respectfully submitted that the grounds for this rejection with respect to claim 41, which is cancelled, are moot, and that claim 49, which is directed to an isolated nucleic acid molecule that comprises a sequence of nucleotides that encodes the sequence of amino acids set forth in SEQ ID No. 15, is outside the purview of this rejection.

Relevant law

See, discussion above

Analysis

The scope of the claims

Claims 27-32 are directed to transgenic *Caenorhabditis* nematodes that contain a vector that contains the nucleic acid encoding the *Caenorhabditis elegans* LOV-1 protein or a mutant thereof that results in altered mating behavior in *Caenorhabditis elegans*.

Claim 41 is cancelled herein

Claim 42 is directed to a transgenic *Caenorhabditis* nematode that contains a mutant *Caenorhabditis elegans* lov-1 gene, where the mutant is one in which a *Caenorhabditis elegans* that expresses it exhibits altered mating behavior.

Claim 49, which is directed to an isolated nucleic acid molecule that comprises a sequence of nucleotides that encodes the sequence of amino acids set forth in SEQ ID No. 15, is outside the purview of this rejection.

Claim 74 is directed to a method for identifying genes or regulatory factors involved in polycystic kidney diseases by mutagenizing transgenic *Caenorhabditis elegans* nematodes that contain a dominant negative *lov-1* transgene and looking for offspring that demonstrate further loss in function and identifying any additional genes responsible for the loss.

Claim 76 is directed to a method for identifying regulators and factors necessary for synthesis and transport of *LOV-1* protein by preparing a transgenic *Caenorhabditis elegans* nematode that expresses a detectable marker linked to *LOV-1* protein, mutagenizing the nematode, selecting nematodes or offspring thereof that have altered patterns of expression of *LOV-1* and identifying the gene responsible for the alteration.

Claim 77 is a method for identifying transcriptional regulators of *lov-1* by preparing a transgenic *Caenorhabditis elegans* nematode that expresses a detectable marker linked to *LOV-1* protein, mutagenizing the nematode, selecting nematodes or offspring thereof that have altered levels of expression of the marker.

Claims 82-84 are directed to methods for identifying genes and regulatory factos involved in polycystic kidney disease by mutagenizing *Caenorhabditis elegans* nematodes, looking for clumping behavior on a lawn of bacteria, selecting males that do not exhibit clumping behavior, mutagenzing them and looking for restoration of wild-type behavior.

Thus, all of the claims specify that the gene is a *Caenorhabditis elegans lov-1* gene and that the behavior that is altered upon mutation thereof is

specified in the claims. Furthermore, claims 74-77 and 82-84 specify that the transgenic nematode is a *Caenorhabditis elegans* nematode.

It is respectfully submitted that the grounds for this rejection with respect to claim 41, which is cancelled, are moot, and that claim 49, which is directed to an isolated nucleic acid molecule that comprises a sequence of nucleotides that encodes the sequence of amino acids set forth in SEQ ID No. 15, is outside the purview of this rejection. Furthermore, claims 74-77 and 82-84, which require the use of transgenic *Caenorhabditis elegans* are outside the purview of his rejection.

It is respectfully submitted that it would not require undue experimentation to introduce the *Caenorhabditis elegans lov-1* gene into a nematode of another *Caenorhabditis* species.

Evaluation of the above-noted factors

Teachings of the specification

The specification describes identification and isolation of the *lov-1* gene from an exemplary nematode, *C. Elegans*, the characterization of *lov-1* mutants, wild-type and mutant LOV-1 proteins encoded by the *lov-1* gene and mutants thereof, the discovery of a correlation between *lov-1* gene expression and observable mating behavior phenotypes, and the use of this discovery in methods to identify genes involved in the etiology of polycystic kidney disease.

The instant application describes and exemplifies in great detail methods for isolating nematode genes, for introducing mutations into nematode genes and for preparing transgenic nematode species.

Further, the specification sets forth assays that correlate expression of *lov-1* nematode mutants with defective mating behaviors, and assays are set forth demonstrating how such correlation may be used to identify genes that are involved in the etiology of polycystic kidney disease.

Level of skill

The level of skill in this art is recognized to be high (see, *e.g.*, Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int'f 1986)). The numerous articles and patents made of record in this application address a highly skilled audience and further evidence the high level of skill in this art.

Knowledge of those of skill in the art

At the time of the effective filing date of this application and before, the skilled artisan knew of standard methods for isolating and characterizing vertebrate homologs of nematode genes. For instance, Bargmann *et al.*, *Science*, 282:2028-2033 (1998), copy attached hereto, discusses that the *C. Elegans* homologs of highly conserved neuronal genes and human disease genes are open to standard methods for isolating mutations and characterizing gene networks by enhancer and suppressor analysis. Brenner, *Genetics*, 77:71-94 (1974), copy attached hereto, describes methods for the isolation, complementation and mapping of *C. Elegans* mutants. A review by the *C. Elegans* Sequencing Consortium of the Washington University Genome Sequencing Center describes the utility of the complete genomic sequence of *C. Elegans* as a platform for investigating biology (*Science*, 282:2012-2018 (1998)).

Further, nematode species that are related to *C. Elegans* are often used in experimental systems to study development at the cellular, genetic and molecular levels. For instance, the aforementioned "Sequencing Consortium" *Science* article describes how, in analyzing the *C. Elegans* sequence, computer-generated gene structure predictions were refined using genomic sequence data from the related nematode *C. Briggsae* (see, page 2013, second full paragraph, col. 2). Further, Sommer *et al.*, Developmental Biology, 173:396-407 (1996) reviews how an understanding of vulval development in *C. Elegans* can be extended to analyze development at the cellular, genetic and molecular levels of three other species of nematodes. Hence those of skill in the art are familiar with a variety of nematode species and manipulation of the genes in those

species and recognize the relatedness among species of the genus *Caenorhabditis*.

Predictability

There is no evidence of record that it is not possible to introduce a gene from one species of nematode into another. The claims only require the *Caenorhabditis* nematode contain the gene (or vector comprising the gene).

Presence of working examples

The specification provides working examples and description for production of transgenic nematodes. The methods are exemplified with *Caenorhabditis elegans*, there is nothing of record to suggest that other *Caenorhabditis* species could not be substituted. As noted above, such species are related.

In contrast, Wall, Houdebine and the other references cited by Examiner describe the unpredictability of transgenic behavior as it relates to unrelated inter-genera predictions, not *intra-genus* behavior of closely related species. The claims merely recite that the instantly claimed *Caenorhabditis* gene is introduced into species of *Caenorhabditis* nematodes.

Conclusion

Therefore, in light of the extensive teachings and examples in the specification, the high level of skill of those in this art, the knowledge of those of skill in the art, the breadth of the claims, it would not require undue experimentation for the skilled artisan to make and use the claimed transgenic *Caenorhabditis* nematodes and to practice the claimed methods.

Also, since it is known that genes among nematodes species are conserved, it would be unfair and unduly limiting to require applicant to limit these claims to *Caenorhabditis elegans*. To do so is contrary to the public policy upon which the U.S. patent laws are based. If applicant is required to limit the claims to only *Caenorhabditis elegans*, then those of skill in the art could by virtue of the teachings of this application readily practice what is

claimed by substituting another *Caenorhabditis* species of nematode, such as *C. briggsae* for the *Caenorhabditis elegans* and practice what is disclosed in the application, but avoid infringing such limited claims. To permit that is simply not fair. T he instant application provides the *lov-1* gene, its role in mating behavior, means for preparation of mutations and assays to identify desired mutations, and the use of the gene and mutant gene to produce transgenic nematodes. Having done so, it is now routine to for others to insert the genes into other *Caenorhabditis* species. Those of skill in the art should not be permitted to make such minor modifications by substitution of a different host and avoid infringing such claims.

Written Description Rejection

Claims 1, 3, 5, 9-11, 15-17, 21-22, 25-32, 41-42, 49, 74-77 and 82-84 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed subject matter.

The Examiner acknowledges that the specification provides adequate written description for the methods and products with regard to the nucleic acid sequence set forth in SEQ ID 3 isolated from *C. Elegans*, nucleic acid molecules that encode the amino acid sequences set forth in SEQ IDs 14 and 15, and a mutant *C. Elegans* that comprises a mutated LOV-1 gene exhibiting a phenotype of defective mating behavior (particularly in the male sensory behaviors response and location of vulva).

The Examiner however states that the specification fails to describe the other nucleic acid molecules that are mutants of or hybridize to SEQ ID NO. 3, other nucleic acid molecules that encode mutant LOV-1, any gene that comprises the nucleic acid sequence of SEQ ID NO. 3, any and all homologs of SEQ ID NO. 3 isolated from any and all nematodes, any and all transgenic nematodes comprising vectors and/or nucleotide sequences, including but not

limited to the sequence set forth in SEQ ID NO. 3, encoding the LOV-1 protein or mutants thereof, and any and all transgenic nematodes that have been mutagenized for use in methods of identifying genes or regulators involved in polycystic kidney disease or that interact with LOV-1. The Examiner further states that it was unknown as of Applicant's effective filing date that any sequences other than the sequence set forth in SEQ ID NO. 3, when constructed and used as claimed, would have the properties of the nucleotide sequence set forth in SEQ ID NO. 3, particularly with regard to the male sensory behaviors response and location of vulva in C. Elegans, or could produce any relevant correlatable phenotype when expressed in a transgenic nematode. Therefore, in the Examiner's estimate, these sequences and methods comprising these sequences lack a written description. Reconsideration of the grounds for this rejection is respectfully requested in view of the amendments herein and the following remarks.

Relevant Law

The purpose behind written description requirement is to ensure that the patent applicant had possessio of the claimed subject mater at the time of filing of the application In re Wertheim, 541 F.2d 257, 262, 191 USPQ 90, 96 (CCPA 1976). The manner in which the specification meets the requirement is not material; it may be met by either an express or an implicit disclosure.

35 U.S.C. §112 requires a written description of the invention. This requirement is distinct from and not coterminous with the enablement requirement:

> The purpose of the 'written description' requirement is broader than to merely explain how to 'make and use'; the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." Vas-Cath, Inc. v. Mahurkar, 935 F.2d at 1563-64, 19 USPQ2d at 1117 (emphasis in original).

The issue with respect to 35 U.S.C. §112, first paragraph, adequate written description has been stated as:

> [d]oes the specification convey clearly to those skilled in the art, to whom it is addressed, in any way, the information that appellants invented that specific compound [claimed embodiment] Vas-Cath, Inc. v. Mahurkar, at 1115, quoting In re Ruschig, 390 F.2d 1990, at 995-996, 154 USPQ 118 at 123 (CCPA 1967).

A specification must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, *i.e.*, whatever is now claimed. Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ.2d 1111, 1117 (Fed. Cir. 1991). A written description requirement issue generally involves the question of whether the subject matter of a claim is supported by or conforms to the disclosure of an application as filed. The test for sufficiency of support in a patent application is whether the disclosure of the application relied upon "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." Ralston Purina Co. v. Far-Mar-Co., Inc., 772 F.2d 1570, 1575, 227 USPQ 177, 179 (Fed. Cir. 1985) (quoting In re Kaslow, 707 F.2d 1366, 1375, 217 USPQ 1089, 1096 (Fed. Cir. 1983)) (see also, MPEP 2163.02).

An objective standard for determining compliance with the written description requirement is "does the description clearly allow persons of skill in the art to recognize that he or she invented what is claimed." In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ.2d 1614, 1618 (Fed. Cir.1989).

The Examiner has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims. In re Wertheim, 541 F.2d 257, 265, 191 USPQ 90, 98 (CCPA 1976); *See also* Ex parte Sorenson, 3 USPQ.2d 1462, 1463 (Bd. Pat.App. & Inter. 1987). By disclosing in a patent application a device that inherently performs a function or has a property, operates according to a theory or has an advantage, a patent application necessarily discloses that function, theory or advantage, even though it says

nothing explicit concerning it. The application may later be amended to recite the function, theory or advantage without introducing prohibited new matter. In re Reynolds, 443 F.2d 384, 170 USPQ 94 (CCPA 1971); and In re Smythe, 480 F. 2d 1376, 178 USPQ 279 (CCPA 1973).

Furthermore, the subject matter of the claim need not be described literally (*i.e.*, using the same terms or *inhaec verba*) in order for the disclosure to satisfy the description requirement. If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application. This conclusion will result in the rejection of the claims affected under 35 U.S.C.112, first paragraph - description requirement, or denial of the benefit of the filing date of a previously filed application, as appropriate.

Analysis

The instant specification provides *Caenorhabditis elegans lov-1* genes and mutants thereof, provides assays for identification of other mutants that confer a readily discernible phenotype , namely, response and location of vulva. The instant application provides exquisitely detailed descriptions and experiments that a) identify the gene in *Caenorhabditis elegans* nematodes; and b) using mutants shows the effects on precisely defined steps in a pathway that results in alterations in mating behavior in nematodes characteristic of each mutation. Furthermore, as is well known to those of skill in this art, and, as described in the application, there is known to be a correspondence between nematode genes and human or other mammalian genes. Hence, nematodes serve as a model system for studying gene pathways and the effects of mutations on such pathways.

For example, at page 4, lines 5-31, the specification describes how mutations in the *lov-1* and *pkd-2* genes of nematodes, such as *C. elegans*, result in two defects in male mating behavior, "response" and "location of vulva":

> **SUMMARY**
> Isolated genes, cDNA and encoded proteins from nematodes that participate in a pathway leading to an observable phenotype are provided. In particular, it is shown herein, that a mutation in *C. elegans*, which gives rise to males that are defective in **certain aspects of mating behavior**, lies in a gene designed herein *lov-1* (location of vulva), and that this gene is an ortholog of the mammalian, particularly human, PKD1 gene. A mutation in a gene designated *pkd-2* herein also gives rise to these behaviors. This gene is shown to be an ortholog of the mammalian, including human, PKD2 gene.
> **The expression pattern of *lov-1* and *pkd-2* was studied and it was found that promoter sequences of both genes cause reporter genes to be expressed in the rays and the hook sensory neurons required for 'response" and vulva location.** Thus showing that the LOV-1 and PKD-2 proteins are involved in chemosensory or mechanosensory signal transduction in sensory neurons. Hence, genes that are components of a pathway in nematodes are provided and are shown to be linked to observable behaviors. (emphasis added)

The claims specify that the lov-1 gene is isolated from a *Caenorhabditis elegans* and in its mutant form confers altered mating behavior. Furthermore, the claims specify that the hybridizing nucleic acids encode a *Caenorhabditis LOV-1* protein, hybridize along their full length under conditions of at least moderate stringency, and, when introduced into *Caenorhabditis elegans* confer wild type behavior.

Therefore applicant had possession of the claimed subject matter at the time of filing of the application.

THE REJECTION OF CLAIMS 1, 3, 5, 7, 9-11, 15-17, 21-22, 25-32 and 41 UNDER 35 U.S.C. §112, SECOND PARAGRAPH

Claims 1, 3, 5, 7, 9-11, 15-17, 21-22, 25-32 and 41 are rejected under 35 U.S.C. 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter that applicants regard as the invention. The Examiner urges that the term "hybridizes" in claim 1 is a relative term which renders the claim indefinite. The Examiner states that the term "hybridizes" is not defined by the claim, the specification does not provide a standard for ascertaining the

requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The Examiner further states that conditions of at least moderate stringency do not sufficiently define the hybridization conditions, as it is not clear if the hybridization assay will detect non-specific hybridization.

This rejection is respectfully traversed insofar as it is applicable to any of the presently pending claims.

First it is noted that the hybridization limitation is not the sole limitation in the claims. The claims require that the nucleic acid molecule comprise a sequence encoding a LOV-1 protein or mutant thereof, a subset of which may hybridize along its full length to the full length of at least one of the exons set forth in SEQ ID NO. 3. Thus, the ability to hybridize, as set forth in the claims, encompasses only those DNA molecules that encode a specific protein, namely, a *Caenorhabditis* LOV-1 protein, and a subset thereof further comprises only those DNA molecules that are sufficiently similar to hybridize under conditions of moderate stringency along their full length to a specific sequence, namely, at least one of the exons set forth in SEQ ID NO. 3. Thus, the extent of non-specific hybridization is defined by the limitations in the claims.

Second, the term "stringency", including the term "moderate stringency" is recognized and understood by those of skill in the art to represent particular conditions. Several utility patents refer to varying degrees of stringency, and conditions therefor. For example, U.S. Patent No. 4,582,788, Apr. 15, 1986 to Erlich, which refers to high stringency as a wash at 0.1 x SSPE, 65° C, describes reduced stringency conditions of 5 x SSPE, 50% formamide, 0.1% SDS, 5 x Denhardt's solution, 200 μg/ml sheared salmon sperm DNA at 37° C to obtain hybridization to related but distinct DNA sequences. U.S. Patent Nos. 4,582,789, Apr. 15, 1986, and 4,617,261, Oct. 14, 1986 to Sheldon, III, et al., refers to a high stringency wash as 0.1 x SSPE, 65° C. In addition, Sheldon, III et al. (see, also U.S. Patent No. 4,705,886, Nov. 10, 1987, to Levenson, et al.) states that:

> hybridization conditions may have varying degrees of stringency depending on the ultimate goal desired. Stringency is affected by temperature, probe length, ionic strength, etc. Changing the concentration of formamide in the solution from about 20% to 50% will alter the polarity and thus the stringency of the hybridization. Generally the hybridization will occur at about 25° to 75° C., preferably 35° to 65° C., for 0.25 to 50 hours, preferably 15-24 hours, these conditions being dependent mainly on the concentration of the specific probe

and nucleic acid sample employed, as well as the concentration of other ingredients in the medium. One skilled in the art of hybridization will be able to make the appropriate adjustments in conditions.

U.S. Patent No. 4,677,063, Jun. 30, 1987, to Mark, et al.. states:

[t]he samples are hybridized with kinased probe under conditions which depend on the stringency desired. Typical moderately stringent conditions employ a temperature of 42° C. for 24-36 hr with 1-5 ml/filter of DNA hybridization buffer containing probe. For higher stringencies high temperatures and shorter times are employed.

U.S. Patent No. 4,681,853, Jul. 21, 1987 Hardy, et al. states:

a hybridization solution using successive washes of increasing stringency. For example, a Standard Saline Phosphate EDTA (IX SSPE) solution containing 0.18 M NaCl, 0.01 M NaPO4 buffer (pH 7.4), and 1 mM EDTA (pH7.4) has been found suitable. The hybridized sheet 48 is washed with successively higher stringency wash solutions. A typical low stringency wash consumes approximately 100 ml of 2X SSPE 1% SDS solution. A typical moderate stringency wash solution consumes about 50 ml of 0.5X SSPE 1% SDS, and a typical high stringency wash solution consumes about 25 ml of 0.1X SSPE 1% SDS.

Those of skill in this art recognize Ausubel et al. ((1987) Current Protocols in Molecular Biology) as defining standard conditions. Ausubel sets forth in great detail stringency conditions for identifying, through hybridization, sequences that are related but not identical to each other such as members of a multigene family, or a similar gene in a second organism. Ausubel describes how to estimate the degree of mismatching that will be tolerated by moderate to low stringency washes relative to a high stringency wash, which destabilizes all mismatched heteroduplexes. Ausubel describes how to estimate the melting temperature (T_m) of a DNA duplex, and, from the value of the Tm, reduce the wash temperature by 1° C per 1% of mismatch desired, or increase the buffer concentration 2-fold for every 17° C change in T_m, and maintain the wash temperature. Ausubel indicates that a low stringency wash is 0.2 x SSC/0.1% SDS at room temperature, a moderate stringency wash is 0.2 x SSC/0.1% SDS at 42° C, and a high stringency wash is 0.1 x SSC/0.1 % SDS at 68° C.

Sellem et al. (1984) Arch. Biochem. Biophys. 229:226-236 describes standard stringent conditions of hybridization as those that tolerate about a 16-17% mismatch.

Those of skill in this art understand the effects of salt and temperature, and other compounds, as formamide, on the stability of hybrids and, therefore, can select equivalent conditions of moderate stringency to identify related gene sequences.

Finally, the term "moderate stringency" is defined in the instant specification (see, page 15, lines 15-20).

Therefore, the term is used consistently by those of skill in the art and is defined in the specification.

Claims 1, 5, 9-11 and 41 are rejected under 35 U.S.C. 112, second paragraph, for indefinite claim language that does not convey a clear meaning, and/or for insufficient antecedent basis in the claims. These objections have been obviated by amendment of the claims and cancellation of claim 41.

THE REJECTION OF CLAIMS 1, 3, 5, 7, 9-11, 15-17 and 41 UNDER 35 U.S.C. § 102

Claims 1, 3, 5, 7, 9-11, 15-17 and 41 are rejected under 35 U.S.C. 102(b) as being allegedly anticipated by Wilson et al., (Nature 368:32-38, 1994) because Wilson discloses *C. Elegans* cosmid clones that comprise over 2.1 Mb of the *C. Elegans* genome that has 100% local similarity to the nucleotide sequence set forth in SEQ ID 3. The Examiner further contends that base pair differences at either end of the cosmid represent mutations that are encompassed in the claims. It is concluded that the disclosure of Wilson *et al.* meets all of the claim limitations. This rejection is respectfully traversed. It is respectfully submitted that this rejection is rendered moot with respect to claims 3 and 41, which are cancelled herein.

Relevant law

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. In re Spada, 15 USPQ2d 1655 (Fed. Cir, 1990), In re Bond, 15 USPQ 1566 (Fed. Cir. 1990), Soundscriber Corp. v. U.S.. 360 F.2d 954, 148 USPQ 298, 301, adopted 149 USPQ 640 (Ct. Cl.) 1966. See, also, Richardson v. Suzuki Motor Co., 868 F.2d 1226, 1236, 9 USPQ2d 1913,1920 (Fed. Cir.), cert. denied, 110 S.Ct. 154 (1989). "[A]ll limitations in the claims must be found in the reference, since the claims measure the invention". In re Lang, 644 F.2d 856, 862, 209 USPQ 288, 293 (CCPA 1981). Moreover it is incumbent on Examiner to identify wherein each and every facet of the claimed invention is disclosed in the

reference. Lindemann Maschinen-fabrik Gmbh v. American Hoist and Derrick Co., 730 F.2d 1452, 221 USPQ 481 (Fed. Cir. 1984).

Further, the reference must describe the invention as claimed sufficiently to have placed a person of ordinary skill in the art in possession of the invention. Prior art does not anticipate a thing or process unless it is enabling; an anticipatory publication must describe the claimed invention with sufficient clarity and specificity so that one skilled in the relevant art could practice the subject matter of the patent without assistance from the patent claimed to have been anticipated Columbia Broadcasting System v. Sylvania Elec. Products, Inc., 415 F.2d 719, 735, 162 USPQ 577 (1st Cir.1968) cert. denied, 396 U.S. 1061, 164 USPQ 321 (1970).

"Before any publication can amount to a statutory bar to the grant of a patent, its disclosure must be such that a skilled artisan could take its teachings in combination with his own knowledge of the particular art and be in possession of the invention." Titanium Metals crp. v Mossinghoff, 603 F.Supp. 87,0, 225 USPQ 673 (1984) quoting In re Application of Le Grice 49 CCPA 1124, 301 F.2d 9333

The claims

Claim 1 is directed to an isolated nucleic acid molecule comprising a sequence encoding a *Caenorhabditis* nematode LOV-1 protein wherein the sequence is selected from among the complement of that set forth in SEQ ID NO. 3, a sequence that hybridizes to SEQ ID NO. 3 under conditions of at least moderate stringency and is present in a nematode genome, or a degenerate nucleotide sequence of SEQ ID NO. 3, and the nematode expressing the protein exhibits normal location of vulva and response sensory behaviors. Claim 5 is directed to the nucleic acid molecule of claim 1 that encodes the amino acid sequence set forth i SEQ ID NO. 4, and claim 7 further defines the nematode of claim 1 as *C. Elegans*. Claim 9 is directed to an isolated gene comprising the nucleic acid molecule of claim 1, and claims 10-11 further defines the isolated gene of claim 9 as comprising homologous or heterologous transcriptional control elements. Claims 15-17 are directed to isolated nucleic acid molecules that encode mutant forms of the protein encoded by the molecule of claim 1 where a *Caenorhabditis elegans* expressing such mutant protein exhibits an alteration in one or both of the location of vulva and/or response phenotype.

Differences between the disclosure of Wilson et al. and the claimed subject matter

Wilson *et al.* discloses *Caenorhabditis elegans* clones, and the GENEFINDER-predicted open reading frames therein. The GENEFINDER program employed in the disclosure of Wilson only identifies likely genes, based on a comparison of the sequence data set forth in Wilson with public sequence databases. Wilson does not disclose the isolated genes, nor mutants thereof, claimed in the instant application. Wilson provides no utility for the encoded open reading frame; it merely provides a sequence of nucleotides. Further, Wilson does not provide any insight into the identity of any gene encoded by the clones. Furthermore, the sequence information set forth in Wilson does not teach or suggest a mutation in the sequence that results in a gene that when expressed in a nematode results in altered mating behavior.

As shown in the instant application, the intron/exon boundaries of isolated genes are not identical to that predicted by computer analysis of the genomic clones in the databases. The cosmid that has 100% local similarity does not encompass the entire *lov-1* gene.

As shown and stated in the application (page 33):

> SEQ ID NO. 3 is the complement of the genomic sequence of the *lov-1* gene. It includes open reading frames (ORFs) between nucleotides 15760 to 27880 of cosmid ZK945 (nucleotides 1 to 12121 of SEQ ID NO.3) and nucleotides 1-564 of cosmid F27E5 (nucleotides 12122 to 12685 of SEQ ID NO.3). **It was found herein, however, that ZK945 and F27E5 overlap from nucleotides 27881 to 27981 and nucleotides 1 to 101, respectively (the overlap region includes nucleotides 12122 to 12222 in SEQ ID NO.3), thereby providing a single, rather than two, ORFs** (emphasis added).

Figure 2b illustrates the intron-exon boundaries of the *lov-1* gene and TABLE 3 provides a summary of their locations with reference to the Sequence Listing. Using RT-PCR with *lov-1* specific primers and *him*-5 mRNA, it was found that *lov-1* encodes one transcript corresponding to Genefinder-predicted ORFs, ZK945.10 and ZK945.9 (Fig. 2b), which had been thought to be two genes. *Lov-1* encodes a predicted 3178 amino acid membrane-bound protein (see SEQ ID Nos. 3 and 4) with a serine-threonine rich extracellular domain homologous to mucins (Carraway *et al.* (1995) *Trends Glycoscience Glycotechnology* 7:31-44), a polycystin homology block 1 (26% identity), and a carboxy terminal polycystin block 2 with 20% identity to

polycystin proteins 1, 2, and 2, encoded by the PKD1, PKD2, and PKDL (polycystic kidney disease) genes, respectively (Fig. 2d).

Furthermore, exons I, J and K were not predicted by GENEFINDER but were identified in the isolated *lov-1* gene (see specification at page 33, line 20 to page 34, line 12), showing that *lov-1* encodes a single transcript rather than what was predicted to be two transcripts. As shown in the application (see, *e.g.*, pages 32 to 35), it was found that *lov-1* encodes one transcript corresponding to Genefinder-predicted ORFs, ZK945.10 and ZK945.9 (Fig. 2b), which had been thought to be two genes:

> DNA sequence analysis of RT-PCR generated cDNA clones from *him-5(e1490)* RNA revealed three exons (**exons I, J and K** in Figure 2B) in the junction between ZK945.10 and ZK945.9: one from nucleotides 25195 to 25742 of the ZK945 cosmid (nucleotides 9436 to 9983 of SEQ ID NO. 3); a second from nucleotides 25071 to 25151 of the ZK945 cosmid (nucleotides 9312 to 9392 of SEQ ID NO. 3); and a third initiating at position 25021 in the ZK945 cosmid (nucleotide 9262 of SEQ ID NO. 3). This demonstrated that the *lov-1* gene encodes one large transcript corresponding to ORFs in ZK945.10 and ZK945.9, spanning what had previously been thought to encode two proteins.

Lov-1 encodes a predicted 3178 amino acid membrane-bound protein that is not described in the Wilson disclosure. Wilson does not describe a single ORF that encodes a 3178 amino acid protein. Hence, the Wilson reference does not provide the *lov-1* gene nor suggest the instantly claimed gene. Therefore, the GENEFINDER-predicted open reading frames disclosed in Wilson do not constitute the isolated nucleic acid molecules claimed in the instant application.

Furthermore, the Wilson disclose any mutations in the sequence, and certainly none that results in a gene that when expressed in a nematode results in altered mating behavior (claim 15 and dependents). As noted, the Wilson disclosure provides no insights regarding the function of this gene and does not teach or suggest any mutations thereof.

Second, the Wilson disclosure does not provide a utility for the sequences disclosed therein; such showing is required for a reference to be novelty defeating. No use is provided for any sequence. Hence, the Wilson reference does not anticipate the instant claims.

Therefore, since anticipation requires that a reference teach all elements as claimed and must provide a utility for a product, Wilson et al. does not anticipate any of claims 1, 3, 5, 7, 9-11 and 15-17.

THE REJECTION OF CLAIMS 1, 3, 5, 7, 9-11, 15-17 and 41 UNDER 35 U.S.C. §103(a)

Claims 1, 3, 5, 7, 9-11, 15-17 and 41 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Hughes *et al.*, *Nature Genetics*, 10:151-160 (1995) taken with Bargmann *et al. Science*, 282:2028-2033 (1998) and Wilson *et al.*, *Nature*, 368:32-38 (1994) because Hughes *et al.* is alleged to teach the identification and characterization of the human polycystic kidney disease PKD1 gene, associated with autosomal dominant polycystic kidney disease. Hughes *et al.* allegedly discuss that it would be a challenge to determine the roles of polycystins both in development and in maintaining adult tissues in the kidney and elsewhere. The Examiner acknowledges that Hughes *et al.* do not teach the *C. Elegans* homolog of PKD1. Bargmann *et al.* allegedly discuss that *C. Elegans* can be a useful system for studying gene pathways, particularly the nervous system, and they compare the *C. Elegans* genes with molecules in the vertebrate nervous system (page 2028). Bargmann allegedly further discusses that the *C. Elegans* homologs of highly conserved neuronal genes and human disease genes are open to standard methods for isolating mutations and characterizing gene networks by enhancer and suppressor analysis (page 2032). Wilson *et al.* allegedly teaches *C. Elegans* cosmid clones that comprise over 2.1 Mb of the *C. Elegans* genome that has 100% local similarity to the nucleotide sequence set forth in SEQ ID 3. The Examiner further contends that base pair differences at either end of the cosmid taught in Wilson represent mutations that are encompassed in the claims.

The Examiner concludes that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the teachings of Hughes et al. to identify a *C. Elegans* homolog of PKD1 in order to elucidate the regulatory pathways of PKD1. The Examiner further contends that one of ordinary skill in the art would have been sufficiently motivated to make such modifications as it was an art recognized goal to elucidate the molecular pathway of polycystic kidney disease in an animal model, particularly *C. Elegans* as discussed by Bargmann *et al.*

This rejection is respectfully traversed. It is respectfully submitted that this rejection is rendered moot with respect to claims 3 and 41, which are cancelled herein.

Relevant law

In order to set forth a prima facie case of obviousness under 35 U.S.C. §103: (1) there must be some teaching, suggestion or incentive supporting the combination of cited references to produce the claimed invention (ACS Hospital Systems, Inc. v. Montefiore Hospital, 732 F.2d 1572, 1577, 221 USPQ 929, 933 (Fed. Cir. 1984)) and (2) the combination of the cited references must actually teach or suggest the claimed invention. Further, that which is within the capabilities of one skilled in the art is not synonymous with that which is obvious. Ex parte Gerlach, 212 USPQ 471 (Bd. APP. 1980). Obviousness is tested by "what the combined teachings of the references would have suggested to those of ordinary skill in the art" In re Keller, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981), but it cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination (ACS Hosp. Systems, Inc. v Montefiore Hosp. 732 F.2d 1572, 1577, 221 USPQ 929, 933 (Fed. Cir. 1984)). "To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher" W.L. Gore & Associates, Inc. v. Garlock Inc., 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983).

The prior art must provide a motivation whereby one of ordinary skill in the art would have been led to do that which the applicant has done. Stratoflex Inc. v Aeroquip Corp., 713 F.2d 1530, 1535, 218 USPQ 871, 876 (Fed. Cir. 1983). In addition, the mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggests the desirability of the modification. In re Fritch, 23 USPQ 1783 (Fed. Cir. 1992).

The prior art can be modified or combined to reject claims as *prima facie* obvious as long as there is a reasonable expectation of success. In re Merck & Co., Inc., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986); and Ex parte Blanc, 13 USPQ2d 1383 (Bd. Pat. App. & Inter. 1989). However, at least some

degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness. In re Rinehart, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976); See also Amgen, Inc. v. Chugai Pharmaceutical Co., 927 F.2d 1200, 1207-08, 18 USPQ2d 1016, 1022-23 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991); and In re O'Farrell, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988). Whether an art is predictable or whether the proposed modification or combination of the prior art has a reasonable expectation of success is determined at the time the invention was made. Ex parte Erlich, 3 USPQ2d 1011, 1016 (Bd. Pat. App. & Inter. 1986).

Also, it is impermissible to ignore the advantages, properties, utilities and unexpected results that flow from the claimed invention; they are part of the invention as a whole. In re Sernaker, 702 F.2d 989, 217 USPQ 1 (Fed. Cir. 1983). Unexpected properties must always be considered when determining obviousness. A compound's structure and properties are inseparable so that unexpected properties are part of the subject matter as a whole. In re Papesh, 315 F.2d 381, 137 USPQ 43 (CCPA 1963).

The claims

Claim 1 is directed to an isolated *Caenorhabditis* nucleic acid molecule comprising a sequence encoding a nematode LOV-1 protein wherein the sequence is selected from among the complement of that set forth in SEQ ID NO. 3, a sequence that hybridizes to SEQ ID NO. 3 under conditions of at least moderate stringency and is present in a nematode genome, or a degenerate nucleotide sequence of SEQ ID NO. 3, and the nematode expressing the protein exhibits normal location of vulva and response sensory behaviors. Claim 5 is directed to the nucleic acid molecule of claim 1 that encodes the amino acid sequence set forth i SEQ ID NO. 4, and claim 7 further defines the nematode of claim 1 as *C. Elegans*. Claim 9 is directed to an isolated gene comprising the nucleic acid molecule of claim 1, and claims 10-11 further defines the isolated

gene of claim 9 as comprising homologous or heterologous transcriptional control elements. Claims 15-17 are directed to isolated nucleic acid molecules that encode mutant forms of the protein encoded by the molecule of claim 1, where a nematode expressing such mutant protein exhibits an alteration in one or both of the location of vulva and response phenotype.

Teachings of the cited references and differences from the claimed subject matter

Primary reference

Hughes *et al.* characterizes the human PKD1 gene involved in autosomal polycystic kidney disease, and the protein encoded by the gene. Hughes teaches that the PKD1 protein appears to be an integral membrane protein involved in cell-cell/matrix interactions. While the Hughes reference concludes with a mention of the need to identify the role of the PKD1 protein, Hughes does not teach or suggest how this may be achieved. Hughes does not teach or suggest an animal model to study the etiology of autosomal polycystic kidney disease.

Secondary references

Bargmann teaches the utility of *C. Elegans* as a model to study several vertebrate homologs inclusing potassium channels, neurotransmitters, ligand-gated ion channels, and G protein-coupled receptors. Bargmann does not teach or suggest the utility of *C. Elegans* in studying the etiology of polycystic kidney disease nor does it teach or suggest nucleic acid molecules that encode the *C. elegans lov-1* gene.

Wilson *et al.* teaches *Caenorhabditis elegans* cosmid clones, and GENEFINDER-predicted open reading frames therein. Wilson does not teach the isolated genes, nor mutants thereof. Further, Wilson does not provide any insight into the identity any gene encoded by the clone. In addition, Wilson does not identify a link between the expression of mutant LOV-1 proteins and altered mating behavior nor a link between its cosmid clones and polycystic kidney diseases. Furthermore, the sequence information set forth in Wilson

does not teach or suggest a mutation in the sequence that results in a gene that when expressed in a nematode results in altered mating behavior.

The Examiner has failed to set forth a prima facie case of obviousness.

Hughes merely identifies a need for discovering the role of PKD1 in the etiology of polycystic kidney disease, but suggests nothing regarding nematodes or a nematode gene. Bargmann describes the use of a *C. Elegans* as a model to study vertebrate genes, but provides no suggestion that there is a nematode homolog for the human PKD1 gene. Wilson teaches a GENEFINDER-predicted open reading frames in the *Caenorhabditis elegans* genome, but does not teach or suggest that among those genes is a gene that is the nematode homlog of the human PKD1 gene nor that such nematode gene is associated with altered mating behaviors.

Hence there is nothing in the combination of teachings of the cited references that would have led the ordinarily skilled artisan to select the open reading frames that turn out to encode the *lov-1* gene. It is only the teachings the instant application that identifies a link between a nematode homolog of the human PKD1 gene involved in autosomal polycystic kidney disease, and its involvement in the response and location of vulva sensory behaviors in the nematode. It is the instant application that identifies a link between mutations in the *lov-1* gene, and altered response and location of vulva mating behaviors in transgenic nematodes expressing these genes.

The combination of the teachings of the primary and secondary references does not lead to the isolated *lov-1* gene claimed in the instant application, which, as discussed earlier, is different from the GENEFINDER-predicted open reading frames disclosed in Wilson *et al.* None of the cited references (primary or secondary) teaches or suggests, singly or in any combination thereof, that the isolated *lov-1* gene from *C. Elegans* would encode a single rather than two transcripts as predicted in Wilson, nor do they teach or

suggest that *C. Elegans* would provide a readily assayable phenotype of the lov-1 gene.

(1) There would have been no motivation to have combined the teachings of the secondary references with the teachings of the primary reference

The primary reference Hughes *et al.* teaches the sequence and structural characteristics of the human PKD1 gene and the encoded protein. There is no mention of the use of *C. Elegans* as a model for studying the etiology of polycystic kidney disease, nor of a possible homolog of the human PKD1 gene in *C. Elegans*. There is, most importantly, no mention that the *C. Elegans* homolog of the human PKD1 gene could be linked to any phenotype, much less that of mating behavior disclosed in the instant application. The secondary references describe the use, in general, of *C. Elegans* as a tool in the study of vertebrate genes (Bargmann), and sequence data from cosmid clones that constitute a portion of the *C. Elegans* genome (Wilson).

There would have been no motivation to have combined the teachings of the secondary references with that of the primary reference, since there is nothing in the Hughes that suggests a combination with Wilson and/or Bargmann.

(2) The combination of teachings of Hughes, Bargmann and Wilson does not result in the instantly claims nucleic acid molecules

Furthermore, absent hindsight reconstruction, the combination of teachings of the references does not result in the presently claimed nucleic acid molecules. As noted above, Hughes does not suggest using nematodes as a model for the study of polycystic kidney disease, does not suggest the existence of a polycystic kidney disease gene homolog in nematodes, much less that there would be an observable nematode phenotype governed by the polycystic kidney disease homolog, and does not suggest the instantly claimed nucleic acid molecules.

The secondary references do not cure these deficiencies. Wilson merely provides sequence of a plurality of cosmid clones, but does not identify any among them that encode the *lov-1* gene of the *Caenorhabditis elegans*. In fact, as noted above, exons I, J and K were not predicted by GENEFINDER but were identified in the isolated *lov-1* gene as disclosed in the instant application.

Hence, the combination of the reference relies on the improper use of hindsight analysis. It is the instant application that provides the suggestion to hunt through the prior art to find the requisite elements of the presently claimed nucleic acid molecules. It is the instant application that identifies the particular cosmid clones, and it is the instant application that provides the missing exons. Therefore, the Examiner has failed to set forth a prima facie case of obviousness.

* * *

In view of the above amendments and remarks, reconsideration and allowance of the application are respectfully requested.

Respectfully submitted,
HELLER EHRMAN WHITE & McAULIFFE LLP

By: _____
Stephanie L. Seidman
Registration No. 33,779

Attorney Docket No. 18021-2919
Address all correspondence to:
HELLER EHRMAN WHITE & McAULIFFE LLP
4350 La Jolla Village Drive, 6th Floor
San Diego, CA 92122
Telephone: 858 450-8400
Facsimile: 858 587-5360
email:sseidman@HEWM.com

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Sternberg *et al.*

Serial No.: 09/479,467

Filed: January 06, 2000

For: POLYCYSTIC KIDNEY DISEASE GENE HOMOLOGS REQUIRED FOR MALE MATING BEHAVIOR IN NEMATODES AND ASSAYS BASED THEREON

Group Art Unit: 1632

Examiner: P. Paras, Jr.

I hereby certify that this paper and the attached papers are being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents Washington, D.C. 20231, on this date.

05/08/01
Date

Stephanie Seidman

MARKED UP CLAIMS (37 C.F.R. § 1.121)

Please amend claims 1, 5, 9, 15, 27, 29, 31, 32, 42, 49, 74, 76, 77, 82 and 83 as follows:

1. (Amended) An isolated nucleic acid molecule, comprising a sequence of nucleotides selected from the group consisting of:

a) a sequence of nucleotides that encodes a *Caenorhabditis* LOV-1 protein and that encodes the sequence of amino acids encoded by [one or more of the exons that is] the complement of the sequence of nucleotides set forth in SEQ ID No. 3; [or]

b) [the] a sequence of nucleotides [set forth as one or more of the exons that are] that is the complement of [the] a sequence of nucleotides set forth in SEQ ID No. 3 and that encodes a *Caenorhabditis* LOV-1 protein, or complement thereof;

c) a sequence of nucleotides that encodes a *Caenorhabditis* LOV-1 gene and that hybridizes along its full length to the full length of at least one of the exons set forth in SEQ ID No. 3 under conditions of at least moderate stringency, and that is present [it]in the genome of a *Caenorhabditis* nematode, wherein a *Caenorhabditis elegans* expressing the LOV-1 protein exhibits normal location of vulva and response male nematode sensory behaviors; [or] and

d) a sequence of nucleotides degenerate with the sequence of nucleotides of c).

5. (Amended) The isolated nucleic acid molecule of claim 1 that comprises a sequence of nucleotides that encodes the sequence of amino acids set forth in SEQ ID No. 4.

9. (Amended) An isolated gene that encodes a nematode LOV-1 protein, comprising the nucleic acid molecule of claim 1.

15. (Amended) An isolated nucleic acid molecule that encodes a mutant *Caenorhabditis* LOV-1 [of the] protein [encoded by the nucleic acid molecule of claim 3], wherein:

[that encodes a nematode LOV-1 protein and] a *Caenorhabditis elegans* nematode expressing the mutant protein exhibits defective mating behavior;

a nematode that expresses such defect exhibits one or both of an altered location of vulva (Lov) and response phenotype; and

a wild-type LOV-1 protein is encoded by the nucleic acid molecule of claim 1.

27. (Amended) A transgenic *Caenorhabditis* species nematode, comprising the vector of claim 26.

29. (Amended) The transgenic nematode of claim 27, wherein: [in] the nematode is *Caenorhabditis elegans* (*C. elegans*); and

the vector or a gene-encoding portion is integrated into the *C. elegans* genome.

31. (Amended) The transgenic nematode of claim 27, wherein:

the nucleic acid molecule encodes a mutant *LOV-1* protein;

a nematode expressing the mutant protein exhibits defective mating behavior;

a nematode that expresses such defect exhibits one or both of an altered location of vulva (Lov) and response phenotype.

32. (Amended) The transgenic nematode of claim 30, wherein: wherein:

the nucleic acid molecule encodes a mutant *LOV-1* protein;

a nematode expressing the mutant protein exhibits defective mating behavior;

a nematode that expresses such defect exhibits one or both of an altered location of vulva (Lov) and response phenotype.

42. (Amended) A transgenic nematode, comprising the nucleic acid molecule of claim [41] 15.

49. (Amended) An isolated nucleic acid molecule of claim [19] 15, comprising a sequence of nucleotides that encodes the sequence of amino acids set forth in SEQ ID No. 15.

74. (Amended) A method for identifying genes or regulatory factors involved in polycystic kidney diseases, comprising:

mutagenizing transgenic *Caenorhabditis elegans* nematodes that contain a dominant negative *lov-1* [or *pkd-2*] transgene;

selecting nematodes or offspring thereof that exhibit a further loss in function of the *lov-1* [or *pkd-2*] transgene by observing mating behaviors; and

identifying the mutations and genes responsible for the loss.

76. (Amended) A method for identifying regulators and factors necessary for synthesis and transport of *LOV-1* [or *PKD-2*] protein;

preparing a transgenic *Caenorhabditis elegans* nematode that expresses a detectable marker linked to *LOV-1* [or *PKD-2*] protein;

mutagenizing the nematode;

selecting nematodes or offspring thereof that have altered patterns of expression of *LOV-1* [or *PKD-2*]; and

identifying the gene responsible for the alteration.

77. (Amended) A method for identifying transcriptional regulators of *lov-1* [or *pkd-2*]; comprising:

preparing a transgenic *Caenorhabditis elegans* nematode that expresses a detectable marker linked to *LOV-1* [or *PKD-2*] protein;

mutagenizing the nematode;

selecting nematodes or offspring thereof that altered levels of expression of the protein.

82. (Amended) [The method of claim 78, wherein:] A method for identifying genes or regulatory factors involved in polycystic kidney diseases, comprising:

treating *Caenorhabditis elegans* nematodes with a test compound or mutagenizing them;

selecting nematodes or the offspring thereof that exhibit altered clumping behavior when seeded on a lawn of bacteria, wherein:

an alteration in the behavior is indicative of change in the genotype of the *lov-1* locus, such that the wild-type males exhibit clumping behavior, and males with a mutation in the *lov-1* locus that alters activity of the LOV-1 protein are randomly dispersed in the bacterial lawn;

mutagenizing the [nematodes are mutant] nematodes that are randomly dispersed in the bacterial lawn; [and then mutagenized]; [and the method further comprises:]

selecting males or the offspring thereof that exhibit a partial or complete restoration of the wild-type behavior;

analyzing the mutations of the males or the offspring thereof that exhibit a partial or complete restoration of the wild-type behavior; and

identifying the genes or mutations responsible for the restoration.

83. (Amended) The method of claim 82, wherein the genes or mutations are genetic supressors of *lov-1* [or *pkd-2*] mutants.